SCHERING CORPORATION

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March 16, 1981

Hearing Clerk
Food and Drug Administration
Department of Health, Education,
and Welfare
Room 4-65
5600 Fishers Lane
Rockville, Maryland 20857

RE: CITIZEN PETITION
Docket No. 76N-0052

Decision on Dosage of
Pseudoephedrine Preparations

Gentlemen:

Pursuant to 21 CFR 10.30, the undersigned companies submit this petition to request that the Commissioner modify the above-referenced decision.

On September 30, 1980, FDA published a notice (45 FR 64709, copy of which is appended hereto) by which the Agency reduced the total adult dosage of pseudoephedrine preparations from 60 mg. every four hours, not to exceed 360 mg. in 24 hours, to 60 mg. every six hours, not to exceed 240 mg. in 24 hours. Although the notice prohibited further interstate shipment of preparations labeled with the former higher dosage after January 30, 1981, that deadline was subsequently extended to May 1, 1981 (45 FR 83671, copy of which is also appended hereto).

A. ACTION REQUESTED

The undersigned companies support the Commissioner's decision to reduce the maximum adult dosage during a 24 hour period from 360 to 240 mg. However, we request that:

(1) the Commissioner reconsider that part of the decision which extends the 60 mg. dosage interval to every six hours and adopt instead a dosage interval of every 4-6 hours; and

(2) the Commissioner extend the deadline of May 1 until such time as the enclosed data have been evaluated and a decision with respect thereto issued, and for a reasonable time thereafter to enable petitioners to revise the labeling for pseudoephedrine products to reflect the Commissioner's final decision.

76N-0052N CP1

76N0052 CP

B. STATEMENT OF GROUNDS

Appended hereto are pharmacokinetic and safety data submitted by petitioners to Dr. William Gilbertson, Mr. Gerald Rachanow and other officials of the Bureau of Drugs on November 12, 1980. Petitioners believe that the pharmacokinetic behavior of pseudoephedrine, both alone and in combination with other drugs, has been further elucidated since the data presented in 1976. It has been found that the major determinant of the half-life of pseudoephedrine is the pH of urine in which pseudoephedrine is excreted. The half-life of pseudoephedrine depending on urine pH has varied in normal individuals from four (4) to eight (8) hours.

In computer simulations of steady state pseudoephedrine concentration profiles as a function of either the every four (4) or six (6) hour dosing schedule, accumulation over time is not a factor, although the steady state profile is a delicate function of the half-life of pseudoephedrine. Thus, the data clearly demonstrate that a flexible dosing schedule of every four (4) to six (6) hours is permissible and more reflective of the achievable blood levels than a fixed dosage of every six (6) hours.

In addition, recent studies afford a reasonable correlation between pseudoephedrine plasma levels and an adverse reaction profile. While small increases in pulse rate can be shown in carefully controlled studies of pseudoephedrine, steady state plasma levels consistent with those derived from simulation do not result in any clinically significant manifestations of these effects.

The pharmacokinetic and safety data submitted with this petition were not available to the Commissioner prior to the notice of September 30, 1980. Petitioners believe these data will alleviate FDA's concerns that pseudoephedrine administered at a lesser interval would result in the accumulation of the drug and eventually marked side effects. These data, which include clinical studies performed by petitioners Burroughs-Wellcome and Dow Chemical, demonstrate that, provided a 240 mg./24 hour limitation is adhered to, a six (6) hour dosage interval provides no safety benefit vis-à-vis the more flexible interval suggested.

Petitioners believe that the interval of every 4-6 hours is consistent with consumer use of pseudoephedrine as a single entity medication and facilitates combination of the drug with other medications.

C. ENVIRONMENTAL IMPACT STATEMENT

Pursuant to 21 CFR 25.1(f)(i), an Environmental Impact Statement need not accompany this petition.

D. ECONOMIC IMPACT ANALYSIS

Pursuant to 21 CFR 10.30, an Economic Impact Analysis need not accompany this petition.

E. CERTIFICATION

The undersigned certify, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes the representative data and information known to the petitioners which are unfavorable to the petition.

Respectfully submitted,

Roberta L. Selman, Esq.
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The Dow Chemical Company
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Food and Drug Administration

[illegible]eeds; Swine Mix Tylan 10 Premix; Withdrawal of Approval of NADA

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: The Food and Drug Administration withdraws approval of a new animal application (NADA) providing for use of Swine Mix Tylan (Tylosin phosphate) 10 Premix in making finished feeds. The feeds are indicated for increased rate of weight gain and improved feed efficiency. The sponsor, Illini Feeds, requested the withdrawal of approval.

EFFECTIVE DATE: December 29, 1980.

FOR FURTHER INFORMATION CONTACT: David N. Scarr, Bureau of Veterinary Medicine (HFV-214), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-1846.

SUPPLEMENTARY INFORMATION: Illini Feeds, Box T, Oneida, IL 61467, is the sponsor of NADA 110-202, which provided for use of a 10-gram-per-pound tylosin premix in making complete swine feeds containing 10 to 100 grams of tylosin per ton. The feeds are indicated for increased rate or weight gain and improved feed efficiency. The NADA was originally approved July 28, 1978. By letter of July 21, 1980, the sponsor requested withdrawal of approval of the NADA because the product has never been manufactured or marketed.

Therefore, under the Federal Food, Drug, and Cosmetic Act (sec. 512(e), 82 Stat. 345-347 (21 U.S.C. 360b(e))), under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.1) and redelegated to the Bureau of Veterinary Medicine (21 CFR 5.84), and in accordance with § 514.115 *Withdrawal of approval of applications* (21 CFR 514.115), notice is given that approval of NADA 110-202 and all supplements for Illini Feeds' Swine Mix Tylan 10 Premix is hereby withdrawn, effective December 29, 1980.

In a separate document published elsewhere in this issue of the **Federal Register**, § 558.625 *Tylosin* is amended by revoking paragraph (b)(55), which provides for approval of this NADA.

Dated: December 3, 1980.

Terence Harvey,

Acting Director, Bureau of Veterinary Medicine.

[FR Doc. [illegible]0120 Filed 12-18-80; 8:45 am]

BILLING CODE 4110-03-M

[Docket No. 76N-0052]

Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-The-Counter (OTC) Human Use; Decision on Dosage of Pseudoephedrine Preparations

AGENCY: Food and Drug Administration, HHS.

ACTION: Extension of effective date.

SUMMARY: The Food and Drug Administration is extending until May 1, 1981, the date by which manufacturers of OTC oral nasal decongestant drug products containing pseudoephedrine are required to comply with FDA's revised dosage limit. The revised labeling would reflect the agency's decision to reduce the maximum daily dosage of pseudoephedrine preparations in the proposed monograph for OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products. The effective date is being changed in response to petitions from two manufacturers who believed that the agency deadline did not allow enough time to reformulate fixed combination products.

DATE: Effective date for required relabeling is May 1, 1981.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Bureau of Drugs (HFD-510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of September 30, 1980 (45 FR 64709), the Commissioner of Food and Drugs announced the decision that the available data did not support the 360-milligram (mg) maximum daily dosage for drug products containing pseudoephedrine for OTC use as an oral nasal decongestant that had been recommended by the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products. The notice explained that data submitted to the agency after the publication of the Panel's proposed monograph suggest that significant side effects could result from the 360-mg daily dosage and that a 240-mg maximum adult daily dosage is more appropriate. The agency concluded that, under the procedures established in 21 CFR 330.13(b)(2), pseudoephedrine products labeled with the higher dosage limitations would be required to be relabeled with specified lower dosage limitations by January 30, 1981.

On October 30, 1980, the Commissioner received two petitions, one from McNeil Consumer Products Co. and the other from Marion Laboratories, Inc., requesting a reconsideration of the January 30, 1981, effective date for the required relabeling. (Copies of the petitions are on file in the Dockets Management Branch (HFA-305), Rm. 4-62, Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.) They based their requests on their belief that the deadline did not allow enough time for changes in fixed combination products, which must be reformulated as well as relabeled to conform to the new reduced dosage limitation. The petitions pointed out that reformulation entails a variety of technical procedures and business transactions that take longer than 4 months to complete. Accordingly, they stated that it would be impossible to reformulate before the announced deadline. Both manufacturers also stressed that there would be increased production costs if current inventories could not be used. The petitions requested that the effective date be extended until either April 1 or May 1, 1981.

The Commissioner has considered these requests and has concluded that good and sufficient reason has been provided for extending the effective date. Therefore, FDA is granting both petitions by extending until May 1, 1981, the effective date for compliance with the revised dosage limitations set forth in the September 30, 1980 notice.

Dated: December 12, 1980.

William F. Randolph,

Acting Associate Commissioner for Regulatory Affairs.

[FR Doc. 80-39425 Filed 12-18-80; 8:45 am]

BILLING CODE 4110-03-M

Ayerst Laboratories; Hycholin Injectable; Withdrawal of Approval of NADA

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: The agency withdraws approval of a new animal drug application (NADA) sponsored by Ayerst Laboratories providing for use of Hycholin (pentapiperide methylsulfate injectable) in management of gastrointestinal disturbances in dogs and cats. The sponsor has requested this action.

EFFECTIVE DATE: December 29, 1980.

FOR FURTHER INFORMATION CONTACT: Howard Meyers, Bureau of Veterinary Medicine (HFV-216), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4093.

SUPPLEMENTARY INFORMATION: Ayerst Laboratories, Division of American Home Products Corp., 685 Third Ave.,

received on or before October 20, 1980, and should be addressed to Mr. John M. Lovelady, Senior Group Director, Regulatory Reports Review, United States General Accounting Office, Room 5106, 441 G Street, NW, Washington, DC 20548.

Further information may be obtained from Patsy J. Stuart of the Regulatory Reports Review Staff, 202-275-3532.

Nuclear Regulatory Commission

The NRC requests an extension without change of the application, reporting and recordkeeping requirements contained in 10 CFR Part 55, Operator's License. Specifically, § 55.10(a) which sets forth the information that must be contained in an application for a nuclear facilities operator's license; § 55.33 which sets forth the requirements for renewal applications for an operator's license; § 55.41 which requires the licensed operator to notify the NRC of any disability which occurs after the submission of his medical certificate; and Appendix A which requires periodic requalification program records be kept to document each licensed operator's or senior operator's participation in the program. The NRC estimates that time to prepare an application under § 55.10(a) will require 1.5 hours and approximately 1,800 will be filed annually; to prepare a renewal application under § 55.33 will require 1.5 hours and approximately 900 will be filed annually; to prepare a notification to NRC of a disability under § 55.41 will require 15 minutes and approximately 15 are expected to be filed annually; and to keep records for the requalification program under Appendix A will require 15 minutes for each record and records are expected to number 900.

Norman F. Heyl,

Regulatory Reports, Review Officer.

[FR Doc. 80-30177 Filed 9-29-80; 8:45 am]

BILLING CODE 1610-01-M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

CENTER FOR DISEASE CONTROL

Mine Health Research Advisory Committee; Meeting

In accordance with Section 10(a)(2) of the Federal Advisory Committee Act (Pub. L. 92-463), the Center for Disease Control announces the following National Institute for Occupational Safety and Health Committee meeting:

Name: Mine Health Research Advisory Committee.

Date: October 30-31, 1980.

Place: Lakeview Inn, Route 6, Morgantown, W. Va. 26505.

Time: 9 a.m.-5:30 p.m., October 30. 8 a.m.-12:30 p.m., October 31.

Type of Meeting: Closed: 9 a.m. to 11:30 a.m. on October 30. Open 1 p.m. on October 30 through adjournment on October 31.

Contact Person: Roy M. Fleming, Sc.D., Executive Secretary, 5600 Fishers Lane, Room 8A-44, Rockville, Md. 20857, Phone: (301) 443-4614.

Purpose: The Committee is charged with advising the Secretary of Health and Human Services on matters involving or relating to mine health research, including grants and contracts for such research.

Agenda: Beginning at 9 a.m. on October 30, the Committee will be performing the final review of the mine health research grant applications for Federal assistance. This portion of the meeting will not be open to the public in accordance with the provisions set forth in Section 552(c)(6), Title 5 U.S. Code and the Determination of the Director, Center for Disease Control, pursuant to Public Law 92-463.

Agenda items for the open portion of the meeting beginning at 1 p.m. on October 30 will include announcements, consideration of minutes of previous meeting and future meeting dates, presentations and discussions on the National Institute for Occupational Safety and Health (NIOSH) program planning process, NIOSH mine research plan and priorities, Bureau of Mines research impacting on health issues, NIOSH response to health hazard evaluation recommendations by the Committe, benzene and lead court decisions, considerations for small population studies, and reports on personal protective equipment and safety workshops.

Agenda items are subject to change as priorities dictate.

The portion of the meeting so indicated is open to the public for observation and participation. Anyone wishing to make an oral presentation should notify the contact person listed above as soon as possible before the meeting. The request should state the amount of time desired, the capacity in which the person will appear, and a brief outline of the presentation. Oral presentations will be scheduled at the discretion of the Chairperson and as time permits. Anyone wishing to have a question answered during the meeting by a scheduled speaker should submit the question in writing, along with his or her name and affiliation, through the Executive Secretary to the Chairperson. At the discretion of the Chairperson and as time permits, appropriate questions will be asked of the speakers.

A roster of members and other relevant information regarding the meeting may be obtained from the contact person listed above.

Dated: September 24, 1980.

William H. Foege, M.D.,

Director, Center for Disease Control.

[FR Doc. 80-30414 Filed 9-29-80; 8:45 am]

BILLING CODE 4110-87-M

Food and Drug Administration

[Docket No. 76N-0052]

Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter (OTC) Human Use; Decision on Dosage of Pseudoephedrine Preparations

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: The Food and Drug Administration is issuing a notice announcing the decision to reduce the dosage of pseudoephedrine preparations (pseudoephedrine hydrochloride and pseudoephedrine sulfate) in the proposed monograph for OTC oral nasal decongestants. This notice also states the agency's interim marketing policy on products containing pseudoephedrine.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Bureau of Drugs (HFD-510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: In the Federal Register of September 9, 1976 (41 FR 38312), the Commissioner of Food and Drugs issued the recommendations and proposed monograph of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products. These recommendations included a determination that pseudoephedrine (pseudoephedrine hydrochloride and pseudoephedrine sulfate) is generally recognized as safe and effective (Category I) for OTC use as an oral nasal decongestant. (See 41 FR 38402.) The Panel recommended an adult oral dosage of 60 milligrams (mg) every 4 hours not to exceed a maximum of 360 mg in 24 hours. This dosage schedule was included in § 341.20(g) of the proposed monograph. (See 41 FR 38420.)

On December 1, 1976, The Dow Chemical Co. submitted data to support the company's request that the Category I adult oral dosage of pseudoephedrine be reduced to 60 mg every 4 to 6 hours not to exceed a maximum of 240 mg in 24 hours (Ref. 1). The company presented data which demonstrated that the half-life of pseudoephedrine is 7 to 8 hours following a 60 mg dose and that a 6-hour dosing schedule will maintain the serum concentration of pseudoephedrine above the peak level achieved following the first single dose (Ref. 2). A study by Bye, Hughes, and Peck (Ref. 3) demonstrated a similar half-life of the 60 mg dosage. Dow Chemical Co. concluded that the data suggest that a maximum dose of 240 mg in 24 hours is a

more appropriate OTC dose than a maximum dose of 360 mg in 24 hours.

Bye, Hughes, and Peck (Ref. 3) also found that a dose of 60 mg pseudoephedrine produced a slight (but not statistically significant) rise in pulse rate which was still evident at 4.5 hours after the first dose and at 6 hours after the second dose. The second dose was given 4.5 hours after the first dose. This would suggest that if another 60 mg had been given at 4 hours after the second dose (as would occur with the Panel's proposed dosage of 60 mg every 4 hours), the pulse rate would have been still higher. This study also demonstrated that when 180 mg of pseudoephedrine in a sustained release dosage form was given twice daily for 14 days, there was a significant increase in heart rate and insomnia for the first 3 days.

Dickerson et al. (Ref. 4) found that 150 mg sustained-release pseudoephedrine taken twice daily caused a greater increase in pulse rate than 120 mg sustained-release pseudoephedrine and that only the higher dose had a significant effect on systolic pressure. Both doses, however, caused a similar incidence of insomnia.

McLaurin, Shipman, and Rosedale (Ref. 5) studied 88 subjects given a single 60-mg dose of pseudoephedrine. Blood pressure, heart rate, subjective responses, and changes in nasal airway obstruction as measured by a rhinometric technique were monitored. No significant differences in any of the measured parameters were apparent. Subjective complaints of nervousness were noted. Multiple-dose studies were not carried out.

Empey et al. (Ref. 6) gave pseudoephedrine 60 mg three times daily for 2 weeks to 40 volunteers with gross pollinosis. Subjective symptom scores were recorded. Pseudopehedrine in a dose of 180 mg daily was significantly effective in reducing symptoms, while side effects were minimal.

Benson (Ref. 7) measured the oral and nasal maximal inspiratory flow rates in eleven volunteers with intermittent nasal obstruction who were given placebo or 60 mg pseudoephedrine in single doses. The study demonstrated that a single dose of drug was followed by significant increase in nasal flow rates lasting up to 2 hours. Multiple dose studies were not done.

References

(1) Dow Chemical Co., Comment submitted on Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic proposed monograph (C–0112) is on file at the Hearing Clerk's office under docket number 76N–0052.

(2) Carski, T. R., "Three-Way Cross Over Study: Comparison of Blood Levels of Pseudoephedrine HCL Following Single Oral Doses of a 120 mg Sustained-Release Formulation with Those Following a Single Oral Dose of a 120 mg Immediate-Release Formulation and with the Levels Following Two Oral Doses of a 60 mg Immediate-Release Formulation," Summary of unpublished study is included in C–0112 cited in Reference (1) above.

(3) Bye, H. M., D. T. D. Hughes, and A. W. Peck, "Comparison of Plasma Levels of L(+) Pseudoephedrine Following Different Formulations, and Their Relation to Cardiovascular and Subjective Effects in Man," *European Journal of Clinical Pharmacology*, 8:47–53, 1975.

(4) Dickerson, J., et al., "Dose Tolerance and Pharmacokinetic Studies of L(+) Pseudoephedrine Capsules in Man," *European Journal of Clinical Pharmacology*, 14:253–259, 1978.

(5) McLaurin, J. W., W. F. Shipman, and R. Rosedale, Jr., "Oral Decongestants. A Double-Blind Comparison Study of the Effectiveness of Four Sympathomimetic Drugs: Objective and Subjective," *Laryngoscope*, 71:54–67, 1961.

(6) Empey, D. W., et al., "A Double-Blind Crossover Trial of Pseudoephedrine and Triprolidine, Alone and in Combination, for the Treatment of Allergic Rhinitis," *Annals of Allergy*, 34:41–46, 1975.

(7) Benson, M. K., "Maximal Nasal Inspiratory Flow Rate: Its Use in Assessing the Effect of Pseudoephedrine in Vasomotor Rhinitis," *European Journal of Clinical Pharmacology*, 3:182–184, 1971.

The agency concludes that the above data do not support the Panel's recommendation for a 360 mg daily dose of pseudoephedrine. In fact, the Carski study (Ref. 2) suggests that a strict 4 hour dosage of 60 mg might lead to accumulation of the drug and eventually marked side effects. The data do, however, support the 60 mg dosage. The data from the studies also suggest that a daily dosage in excess of 240 mg of pseudoephedrine may be associated with significant side effects without additional therapeutic benefit. Therefore, the agency concludes that there are sufficient data to support a 60 mg dose of pseudoephedrine every 6 hours with a maximum 24 hour dose of 240 mg. The agency also points out that the Panel recommended an oral dosage for pseudoephedrine preparations for children 6 to under 12 years of age of 30 mg every 4 hours not to exceed 180 mg in 24 hours and for children 2 to under 6 years of age of 15 mg every 4 hours not to exceed 90 mg in 24 hours. These maximum daily dosages are one-half and one-quarter of the adult maximum daily dose. Along with the reduction in the adult maximum daily dose to 240 mg, the agency is also reducing the dosages for children proportionately. The new dosage for children 6 to under 12 years of age will be 30 mg every 6 hours not to exceed 120 mg in 24 hours and for children 2 to under 6 years of age will be 15 mg every 6 hours not to exceed 60 mg in 24 hours.

The OTC drug review regulations in § 330.13 (21 CFR 330.13) state the conditions for marketing on OTC drug product containing an active ingredient at a dosage level higher than that available in an OTC drug product on December 4, 1975, which an OTC Advisory Review Panel has recommended for OTC use. These regulations allow the OTC marketing of such a product at the higher dosage level after the date of publication in the **Federal Register** of the Panel's report and proposed monograph, subject to the risk that the Commissioner may not accept the Panel's recommendation and may instead adopt a different position that may require relabeling, recall, or other regulatory action. The OTC marketing of products containing pseudoephedrine labeled with a 60-mg single dose or a maximum daily dose of 360 mg represents marketing of an active ingredient at a dosage level higher than that available in an OTC drug product on December 4, 1975. Under the provisions of § 330.13(b)(2), such products labeled in accord with the proposed monograph may be marketed unless the Commissioner adopts and announces a different position. In this notice, the Commissioner is announcing that he does not, at this time, accept the recommendation of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products on the dosage of drug products containing pseudoephedrine for OTC use as an oral nasal decongestant. As provided under § 330.13(b)(2), the Commissioner has concluded that OTC drug products marketed for use as an oral nasal decongestant containing pseudoephedrine at a dosage level higher than that available in an OTC drug product on December 4, 1975 are required to be labeled with the following dosage limitations:

Adult oral dosage is 60 mg every 6 hours not to exceed 240 mg in 24 hours. For children 6 to under 12 years of age, the oral dosage is 30 mg every 6 hours not to exceed 120 mg in 24 hours. For children 2 to under 6 years of age, the oral dosage is 15 mg every 6 hours not to exceed 60 mg in 24 hours. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician.

Therefore, in accordance with § 330.13(b)(2), any OTC oral nasal decongestant drug product containing pseudoephedrine at a dosage level higher than that available in an OTC drug product on December 4, 1975 is required to be labeled with this new

lower dosage. To avoid disruption of the OTC cough-cold market, firms will be allowed up to 4 months, until January 30, to relabel their OTC oral nasal decongestant drug products containing pseudoephedrine. Manufacturers are encouraged, however, to implement this change in the labeling of currently marketed products containing pseudoephedrine at the earliest possible time. After January 30, 1981, no further shipments of OTC oral nasal decongestant drug products containing pseudoephedrine labeled with the former higher dosage can be initially introduction or initially delivered for introduced into interstate commerce.

The agency will include these revised dosages for pseudoephedrine preparations in the tentative final monograph on OTC nasal decongestant drug products. The agency intends to issue the tentative final monograph for OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products in segments. The first segment will be on anticholinergics and expectorants. Subsequent sections will be published on antihistamines, nasal decongestants, antitussives, bronchodilators, and combinations. A final determination of the appropriate dosage limitations for OTC pseudoephedrine preparations will be made in the final monograph for these nasal decongestant drug products.

Dated: September 22, 1980.

William F. Randolph,

Acting Associate Commissioner for Regulatory Affairs.

[FR Doc. 80-29912 Filed 9-29-80; 8:45 am]

BILLING CODE 4110-03-M

[Docket No. 80D-0217]

General Statistical Documentation Guide for Protocol Development of NDA Submissions, Availability of Draft Guideline; Extension of Comment Period

AGENCY: Food and Drug Administration.

ACTION: Extension of comment period.

SUMMARY: The Food and Drug Administration (FDA) is extending the period for submitting comments on the draft guideline entitled "General Statistical Documentation Guide for Protocol Development and NDA Submissions." This action is in response to a request by the Pharmaceutical Manufacturers Association for additional time to consider the draft guideline and prepare comments. FDA believes it is in the public interest to ... final preparation of the guideline ... the Pharmaceutical Manufacturers Association's comments can be reviewed.

DATE: Written comments by December 6, 1980.

ADDRESS: Written comments to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Satya D. Dubey, Bureau of Drugs (HFD-232), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4594.

SUPPLEMENTARY INFORMATION: In the Federal Register of July 8, 1980 (45 FR 45961), FDA announced the availability of a draft guideline entitled "General Statistical Documentation Guide for Protocol Development and NDA Submission," prepared by FDA's Bureau of Drugs, which sets forth the type of material needed to permit statistical review of protocols and completed clinical studies by the agency. Interested persons were given until October 6, 1980, to submit written comments on the guideline. In response to a request from the Pharmaceutical Manufacturers Association, FDA is extending the comment period for all interested persons until December 6, 1980.

Interested persons may, on or before December 6, 1980, submit written comments on the draft guideline to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857. Those comments will be considered in determining whether further amendments to or revisions of the guideline are warranted. Comments should be in four copies (except that individuals may submit single copies), identified with the Hearing Clerk docket number found in brackets in the heading of this document. The draft guideline and received comments may be seen in the Hearing Clerk's office between 9 a.m. and 4 p.m., Monday through Friday.

Dated: September 23, 1980.

William F. Randolph,

Acting Associate Commissioner for Regulatory Affairs.

[FR Doc. 80-30207 Filed 9-26-80; 9:55 am]

BILLING CODE 4110-03-M

Public Health Service

Privacy Act of 1974; New System of Records

AGENCY: Department of Health and Human Services; Public Health Service.

ACTION: Waiver of advance notice period for a new system of records.

SUMMARY: FR Doc. 80-26614, appearing at page 58209 in the issue for Tuesday, September 2, 1980, provided notification of a new system of records proposed by the Health Resources Administration. That system is 09-35-0045, "Nurse Practitioner Traineeships," HHS/HRA/BHPr. The document stated that the Public Health Service (PHS) had requested that the Office of Management and Budget (OMB) grant a waiver of the usual requirement that a system of records not be put into effect until 60 days after the report is sent to OMB and Congress.

OMB granted the requested waiver on September 12, 1980. Accordingly, system of records number 09-35-0045 became effective upon the date of the waiver. However, PHS will not disclose information from this system pursuant to a routine use until after the period for public comment on proposed routine uses elapses on October 2, 1980.

Dated: September 23, 1980.

Jack N. Markowitz,

Acting Director, Office of Management.

[FR Doc. 80-199 Filed 9-29-80; 8:45 am]

BILLING CODE 4110-85-M

DEPARTMENT OF HOUSING AND URBAN DEVELOPMENT

Office of the Assistant Secretary for Community Planning and Development

[Docket No. N-80-1028]

Community Development Block Grant Program for Indian Tribes and Alaskan Natives

AGENCY: Housing and Urban Development/Office of the Assistant Secretary for Community Planning and Development.

ACTION: Notice.

SUMMARY: This notice sets the deadline for filing pre-applications for Community Development Block Grant Funds for Indian Tribes and Alaskan Natives for Fiscal Year 1981. Pre-applications are required in order to provide HUD with sufficient information to determine which applicants will be invited to submit full application and to save applicants the cost of preparing full applications which have no chance of being funded.

SUPPLEMENTARY INFORMATION: This notice sets the deadline for submitting pre-applications as provided in 24 CFR 571.301 published by final rule on December 15, 1978 (43 FR 58734). That rule established Part 571 as a separate part applying the Community Development Block Grant Program to

received on or before October 20, 1980, and should be addressed to Mr. John M. Lovelady, Senior Group Director, [illegible]itory Reports Review, United States General Accounting Office, Room 5106, 441 G Street, NW, Washington, DC 20548.

Further information may be obtained from Patsy J. Stuart of the Regulatory Reports Review Staff, 202–275–3532.

Nuclear Regulatory Commission

The NRC requests an extension without change of the application, reporting and recordkeeping requirements contained in 10 CFR Part 55, Operator's License. Specifically, § 55.10(a) which sets forth the information that must be contained in an application for a nuclear facilities operator's license; § 55.33 which sets forth the requirements for renewal applications for an operator's license; § 55.41 which requires the licensed operator to notify the NRC of any disability which occurs after the submission of his medical certificate; and Appendix A which requires periodic requalification program records be kept to document each licensed operator's or senior operator's participation in the program. The NRC estimates that time to prepare an application under § 55.10(a) will require 1.5 hours and approximately 1,800 will be filed [illegible]lly; to prepare a renewal application under § 55.33 will require 1.5 hours and approximately 900 will be filed annually; to prepare a notification to NRC of a disability under § 55.41 will require 15 minutes and approximately 15 are expected to be filed annually; and to keep records for the requalification program under Appendix A will require 15 minutes for each record and records are expected to number 900.

Norman F. Heyl,

Regulatory Reports, Review Officer.

[FR Doc. 80-30177 Filed 9-29-80; 8:45 am]

BILLING CODE 1610-01-M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

CENTER FOR DISEASE CONTROL

Mine Health Research Advisory Committee; Meeting

In accordance with Section 10(a)(2) of the Federal Advisory Committee Act (Pub. L. 92–463), the Center for Disease Control announces the following National Institute for Occupational Safety and Health Committee meeting:

Name: Mine Health Research Advisory [illegible]mittee.

Dates: October 30–31, 1980.

Place: Lakeview Inn, Route 6, Morgantown, W. Va. 26505.

Time: 9 a.m.–5:30 p.m., October 30. 8 a.m.–12:30 p.m., October 31.

Type of Meeting: Closed: 9 a.m. to 11:30 a.m. on October 30. Open 1 p.m. on October 30 through adjournment on October 31.

Contact Person: Roy M. Fleming, Sc.D., Executive Secretary, 5600 Fishers Lane, Room 8A–44, Rockville, Md. 20857, Phone: (301) 443–4614.

Purpose: The Committee is charged with advising the Secretary of Health and Human Services on matters involving or relating to mine health research, including grants and contracts for such research.

Agenda: Beginning at 9 a.m. on October 30, the Committee will be performing the final review of the mine health research grant applications for Federal assistance. This portion of the meeting will not be open to the public in accordance with the provisions set forth in Section 552(c)(6), Title 5 U.S. Code and the Determination of the Director, Center for Disease Control, pursuant to Public Law 92–463.

Agenda items for the open portion of the meeting beginning at 1 p.m. on October 30 will include announcements, consideration of minutes of previous meeting and future meeting dates, presentations and discussions on the National Institute for Occupational Safety and Health (NIOSH) program planning process, NIOSH mine research plan and priorities, Bureau of Mines research impacting on health issues, NIOSH response to health hazard evaluation recommendations by the Committe, benzene and lead court decisions, considerations for small population studies, and reports on personal protective equipment and safety workshops.

Agenda items are subject to change as priorities dictate.

The portion of the meeting so indicated is open to the public for observation and participation. Anyone wishing to make an oral presentation should notify the contact person listed above as soon as possible before the meeting. The request should state the amount of time desired, the capacity in which the person will appear, and a brief outline of the presentation. Oral presentations will be scheduled at the discretion of the Chairperson and as time permits. Anyone wishing to have a question answered during the meeting by a scheduled speaker should submit the question in writing, along with his or her name and affiliation, through the Executive Secretary to the Chairperson. At the discretion of the Chairperson and as time permits, appropriate questions will be asked of the speakers.

A roster of members and other relevant information regarding the meeting may be obtained from the contact person listed above.

Dated: September 24, 1980.

William H. Foege, M.D.,

Director, Center for Disease Control.

[FR Doc. 80-30414 Filed 9-29-80; 8:45 am]

BILLING CODE 4110-87-M

Food and Drug Administration

[Docket No. 76N-0052]

Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter (OTC) Human Use; Decision on Dosage of Pseudoephedrine Preparations

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: The Food and Drug Administration is issuing a notice announcing the decision to reduce the dosage of pseudoephedrine preparations (pseudoephedrine hydrochloride and pseudoephedrine sulfate) in the proposed monograph for OTC oral nasal decongestants. This notice also states the agency's interim marketing policy on products containing pseudoephedrine.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Bureau of Drugs (HFD–510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–443–4960.

SUPPLEMENTARY INFORMATION: In the Federal Register of September 9, 1976 (41 FR 38312), the Commissioner of Food and Drugs issued the recommendations and proposed monograph of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products. These recommendations included a determination that pseudoephedrine (pseudoephedrine hydrochloride and pseudoephedrine sulfate) is generally recognized as safe and effective (Category I) for OTC use as an oral nasal decongestant. (See 41 FR 38402.) The Panel recommended an adult oral dosage of 60 milligrams (mg) every 4 hours not to exceed a maximum of 360 mg in 24 hours. This dosage schedule was included in § 341.20(g) of the proposed monograph. (See 41 FR 38420.)

On December 1, 1976, The Dow Chemical Co. submitted data to support the company's request that the Category I adult oral dosage of pseudoephedrine be reduced to 60 mg every 4 to 6 hours not to exceed a maximum of 240 mg in 24 hours (Ref. 1). The company presented data which demonstrated that the half-life of pseudoephedrine is 7 to 8 hours following a 60 mg dose and that a 6-hour dosing schedule will maintain the serum concentration of pseudoephedrine above the peak level achieved following the first single dose (Ref. 2). A study by Bye, Hughes, and Peck (Ref. 3) demonstrated a similar half-life of the 60 mg dosage. Dow Chemical Co. concluded that the data suggest that a maximum dose of 240 mg in 24 hours is a

more appropriate OTC dose than a maximum dose of 360 mg in 24 hours.

Bye, Hughes, and Peck (Ref. 3) also found that a dose of 60 mg pseudoephedrine produced a slight (but not statistically significant) rise in pulse rate which was still evident at 4.5 hours after the first dose and at 6 hours after the second dose. The second dose was given 4.5 hours after the first dose. This would suggest that if another 60 mg had been given at 4 hours after the second dose (as would occur with the Panel's proposed dosage of 60 mg every 4 hours), the pulse rate would have been still higher. This study also demonstrated that when 180 mg of pseudoephedrine in a sustained release dosage form was given twice daily for 14 days, there was a significant increase in heart rate and insomnia for the first 3 days.

Dickerson et al. (Ref. 4) found that 150 mg sustained-release pseudoephedrine taken twice daily caused a greater increase in pulse rate than 120 mg sustained-release pseudoephedrine and that only the higher dose had a significant effect on systolic pressure. Both doses, however, caused a similar incidence of insomnia.

McLaurin, Shipman, and Rosedale (Ref. 5) studied 88 subjects given a single 60-mg dose of pseudoephedrine. Blood pressure, heart rate, subjective responses, and changes in nasal airway obstruction as measured by a rhinometric technique were monitored. No significant differences in any of the measured parameters were apparent. Subjective complaints of nervousness were noted. Multiple-dose studies were not carried out.

Empey et al. (Ref. 6) gave pseudoephedrine 60 mg three times daily for 2 weeks to 40 volunteers with gross pollinosis. Subjective symptom scores were recorded. Pseudopehedrine in a dose of 180 mg daily was significantly effective in reducing symptoms, while side effects were minimal.

Benson (Ref. 7) measured the oral and nasal maximal inspiratory flow rates in eleven volunteers with intermittent nasal obstruction who were given placebo or 60 mg pseudoephedrine in single doses. The study demonstrated that a single dose of drug was followed by significant increase in nasal flow rates lasting up to 2 hours. Multiple dose studies were not done.

References

(1) Dow Chemical Co., Comment submitted on Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic proposed monograph (C–0112) is on file at the Hearing Clerk's office under docket number 76N–0052.

(2) Carski, T. R., "Three-Way Cross Over Study: Comparison of Blood Levels of Pseudoephedrine HCL Following Single Oral Doses of a 120 mg Sustained-Release Formulation with Those Following a Single Oral Dose of a 120 mg Immediate-Release Formulation and with the Levels Following Two Oral Doses of a 60 mg Immediate-Release Formulation," Summary of unpublished study is included in C–0112 cited in Reference (1) above.

(3) Bye, H. M., D. T. D. Hughes, and A. W. Peck, "Comparison of Plasma Levels of L(+) Pseudoephedrine Following Different Formulations, and Their Relation to Cardiovascular and Subjective Effects in Man," *European Journal of Clinical Pharmacology*, 8:47–53, 1975.

(4) Dickerson, J., et al., "Dose Tolerance and Pharmacokinetic Studies of L(+) Pseudoephedrine Capsules in Man," *European Journal of Clinical Pharmacology*, 14:253–259, 1978.

(5) McLaurin, J. W., W. F. Shipman, and R. Rosedale, Jr., "Oral Decongestants. A Double-Blind Comparison Study of the Effectiveness of Four Sympathomimetic Drugs: Objective and Subjective," *Laryngoscope*, 71:54–67, 1961.

(6) Empey, D. W., et al., "A Double-Blind Crossover Trial of Pseudoephedrine and Triprolidine, Alone and in Combination, for the Treatment of Allergic Rhinitis," *Annals of Allergy*, 34:41–46, 1975.

(7) Benson, M. K., "Maximal Nasal Inspiratory Flow Rate: Its Use in Assessing the Effect of Pseudoephedrine in Vasomotor Rhinitis," *European Journal of Clinical Pharmacology*, 3:182–184, 1971.

The agency concludes that the above data do not support the Panel's recommendation for a 360 mg daily dose of pseudoephedrine. In fact, the Carski study (Ref. 2) suggests that a strict 4 hour dosage of 60 mg might lead to accumulation of the drug and eventually marked side effects. The data do, however, support the 60 mg dosage. The data from the studies also suggest that a daily dosage in excess of 240 mg of pseudoephedrine may be associated with significant side effects without additional therapeutic benefit. Therefore, the agency concludes that there are sufficient data to support a 60 mg dose of pseudoephedrine every 6 hours with a maximum 24 hour dose of 240 mg. The agency also points out that the Panel recommended an oral dosage for pseudoephedrine preparations for children 6 to under 12 years of age of 30 mg every 4 hours not to exceed 180 mg in 24 hours and for children 2 to under 6 years of age of 15 mg every 4 hours not to exceed 90 mg in 24 hours. These maximum daily dosages are one-half and one-quarter of the adult maximum daily dose. Along with the reduction in the adult maximum daily dose to 240 mg, the agency is also reducing the dosages for children proportionately. The new dosage for children 6 to under 12 years of age will be 30 mg every 6 hours not to exceed 120 mg in 24 hours and for children 2 to under 6 years of age will be 15 mg every 6 hours not to exceed 60 mg in 24 hours.

The OTC drug review regulations in § 330.13 (21 CFR 330.13) state the conditions for marketing on OTC drug product containing an active ingredient at a dosage level higher than that available in an OTC drug product on December 4, 1975, which an OTC Advisory Review Panel has recommended for OTC use. These regulations allow the OTC marketing of such a product at the higher dosage level after the date of publication in the Federal Register of the Panel's report and proposed monograph, subject to the risk that the Commissioner may not accept the Panel's recommendation and may instead adopt a different position that may require relabeling, recall, or other regulatory action. The OTC marketing of products containing pseudoephedrine labeled with a 60-mg single dose or a maximum daily dose of 360 mg represents marketing of an active ingredient at a dosage level higher than that available in an OTC drug product on December 4, 1975. Under the provisions of § 330.13(b)(2), such products labeled in accord with the proposed monograph may be marketed unless the Commissioner adopts and announces a different position. In this notice, the Commissioner is announcing that he does not, at this time, accept the recommendation of the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products on the dosage of drug products containing pseudoephedrine for OTC use as an oral nasal decongestant. As provided under § 330.13(b)(2), the Commissioner has concluded that OTC drug products marketed for use as an oral nasal decongestant containing pseudoephedrine at a dosage level higher than that available in an OTC drug product on December 4, 1975 are required to be labeled with the following dosage limitations:

Adult oral dosage is 60 mg every 6 hours not to exceed 240 mg in 24 hours. For children 6 to under 12 years of age, the oral dosage is 30 mg every 6 hours not to exceed 120 mg in 24 hours. For children 2 to under 6 years of age, the oral dosage is 15 mg every 6 hours not to exceed 60 mg in 24 hours. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a physician.

Therefore, in accordance with § 330.13(b)(2), any OTC oral nasal decongestant drug product containing pseudoephedrine at a dosage level higher than that available in an OTC drug product on December 4, 1975 is required to be labeled with this new

lower dosage. To avoid disruption of the OTC cough-cold market, firms will be allowed up to 4 months, until January 30, [illegible] to relabel their OTC oral nasal decongestant drug products containing pseudoephedrine. Manufacturers are encouraged, however, to implement this change in the labeling of currently marketed products containing pseudoephedrine at the earliest possible time. After January 30, 1981, no further shipments of OTC oral nasal decongestant drug products containing pseudoephedrine labeled with the former higher dosage can be initially introduction or initially delivered for introduced into interstate commerce.

The agency will include these revised dosages for pseudoephedrine preparations in the tentative final monograph on OTC nasal decongestant drug products. The agency intends to issue the tentative final monograph for OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products in segments. The first segment will be on anticholinergics and expectorants. Subsequent sections will be published on antihistamines, nasal decongestants, antitussives, bronchodilators, and combinations. A final determination of the appropriate dosage limitations for OTC pseudoephedrine preparations will be made in the final monograph for these nasal decongestant drug products.

Dated: September 22, 1980.

William F. Randolph,

Acting Associate Commissioner for Regulatory Affairs.

[FR Doc. 80-29912 Filed 9-29-80; 8:45 am]

BILLING CODE 4110-03-M

[Docket No. 80D-0217]

General Statistical Documentation Guide for Protocol Development of NDA Submissions, Availability of Draft Guideline; Extension of Comment Period

AGENCY: Food and Drug Administration.

ACTION: Extension of comment period.

SUMMARY: The Food and Drug Administration (FDA) is extending the period for submitting comments on the draft guideline entitled "General Statistical Documentation Guide for Protocol Development and NDA Submissions." This action is in response to a request by the Pharmaceutical Manufacturers Association for additional time to consider the draft guideline and prepare comments. FDA believes it is in the public interest to [illegible]y final preparation of the guideline [illegible] the Pharmaceutical Manufacturers Association's comments can be reviewed.

DATE: Written comments by December 6, 1980.

ADDRESS: Written comments to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Satya D. Dubey, Bureau of Drugs (HFD-232), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4594.

SUPPLEMENTARY INFORMATION: In the Federal Register of July 8, 1980 (45 FR 45961), FDA announced the availability of a draft guideline entitled "General Statistical Documentation Guide for Protocol Development and NDA Submission," prepared by FDA's Bureau of Drugs, which sets forth the type of material needed to permit statistical review of protocols and completed clinical studies by the agency. Interested persons were given until October 6, 1980, to submit written comments on the guideline. In response to a request from the Pharmaceutical Manufacturers Association, FDA is extending the comment period for all interested persons until December 6, 1980.

Interested persons may, on or before December 6, 1980, submit written comments on the draft guideline to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857. Those comments will be considered in determining whether further amendments to or revisions of the guideline are warranted. Comments should be in four copies (except that individuals may submit single copies), identified with the Hearing Clerk docket number found in brackets in the heading of this document. The draft guideline and received comments may be seen in the Hearing Clerk's office between 9 a.m. and 4 p.m., Monday through Friday.

Dated: September 23, 1980.

William F. Randolph,

Acting Associate Commissioner for Regulatory Affairs.

[FR Doc. 80-30207 Filed 9-26-80; 9:55 am]

BILLING CODE 4110-03-M

Public Health Service

Privacy Act of 1974; New System of Records

AGENCY: Department of Health and Human Services; Public Health Service.

ACTION: Waiver of advance notice period for a new system of records.

SUMMARY: FR Doc. 80-26614, appearing at page 58209 in the issue for Tuesday, September 2, 1980, provided notification of a new system of records proposed by the Health Resources Administration. That system is 09-35-0045, "Nurse Practitioner Traineeships," HHS/HRA/BHPr. The document stated that the Public Health Service (PHS) had requested that the Office of Management and Budget (OMB) grant a waiver of the usual requirement that a system of records not be put into effect until 60 days after the report is sent to OMB and Congress.

OMB granted the requested waiver on September 12, 1980. Accordingly, system of records number 09-35-0045 became effective upon the date of the waiver. However, PHS will not disclose information from this system pursuant to a routine use until after the period for public comment on proposed routine uses elapses on October 2, 1980.

Dated: September 23, 1980.

Jack N. Markowitz,

Acting Director, Office of Management.

[FR Doc. 80-199 Filed 9-29-80; 8:45 am]

BILLING CODE 4110-85-M

DEPARTMENT OF HOUSING AND URBAN DEVELOPMENT

Office of the Assistant Secretary for Community Planning and Development

[Docket No. N-80-1028]

Community Development Block Grant Program for Indian Tribes and Alaskan Natives

AGENCY: Housing and Urban Development/Office of the Assistant Secretary for Community Planning and Development.

ACTION: Notice.

SUMMARY: This notice sets the deadline for filing pre-applications for Community Development Block Grant Funds for Indian Tribes and Alaskan Natives for Fiscal Year 1981. Pre-applications are required in order to provide HUD with sufficient information to determine which applicants will be invited to submit full application and to save applicants the cost of preparing full applications which have no chance of being funded.

SUPPLEMENTARY INFORMATION: This notice sets the deadline for submitting pre-applications as provided in 24 CFR 571.301 published by final rule on December 15, 1978 (43 FR 58734). That rule established Part 571 as a separate part applying the Community Development Block Grant Program to

PSEUDOEPHEDRINE DOSAGE INTERVAL
Data to support Citizen Petition
dated March 16, 1981 and
submitted by:

The Dow Chemical Company
Burroughs-Wellcome Co.
Schering Corporation

Pseudoephedrine was introduced in the U.S. market as an orally effective nasal decongestant by Burroughs Wellcome in the 1930's. While pseudoephedrine is not the only oral nasal decongestant available, the amount of published and unpublished data on the safety and efficacy of this compound far exceeds that available for any other drug in this class (see attached references).*

In the publication of the proposed OTC Cough/Cold Bronchodilator Anti-Allergy Drug Monograph (Federal Register Vol. 41: 38402, September 9, 1976), pseudoephedrine was recognized to be safe and efficacious as a single entity drug, and as an ingredient of rational drug mixtures as outlined by the panel (see Appendix I). The recommended adult oral dose for pseudoephedrine in the original OTC Monograph was 60 mg every 4 hours, not to exceed 360 mg in 24 hours. Following the publication of this monograph, comments were submitted (Appendix 2) which, while in basic agreement with the panel recommendations, questioned the maximum allowable daily dose. The basis for these comments were twofold: 1) little experience existed concerning daily doses in excess of 240 mg per 24 hours, and 2) pharmacokinetic data available in 1976 did not adequately predict the behavior of this compound dosed at 360 mg per day.

As a result of the aforementioned comments, revised dosage guidelines were published (Federal Register Vol. 45:64709, September 30, 1980) to amend the total daily recommended dose to 240 mg in 24 hours. However, in these

* A bibliography of all cited references follows the Appendices. Copies of the individual papers follow the bibliography.

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recommendations the dosage interval for pseudoephedrine as a safe and effective OTC drug was fixed at a strict 6 hours. The concerns which prompted such action resulted from the following considerations:
1) preliminary pharmacokinetic data presented in 1976 suggested that pseudoephedrine would accumulate if the drug were given every 4 hours; and
2) the possibility of clinically significant cardiovascular effects of pseudoephedrine which appeared to be dose related.

New data which may not have been available to the Agency do much to eliminate the concerns outlined above. These confirm that if a 240 mg/24 hour limit is observed, a strict 6 hour dosing interval confers no added safety benefit relative to a more flexible interval (e.g. 4-6 hours). Furthermore, a 6 hour interval is inconsistent with consumer use of the product as a single entity medication and renders the combination of pseudoephedrine with other medications exceedingly difficult. Consequently we are proposing that the OTC dosage interval for pseudoephedrine be every 4-6 hours with a maximum allowable adult dose of 240 mg/24 hours. Evidence supporting our proposal is presented below.

PHARMACOKINETIC DATA - COMPUTER SIMULATION OF STEADY STATE PSEUDOEPHEDRINE CONCENTRATION PROFILES AS A FUNCTION OF DOSAGE INTERVAL

The pharmacokinetic behavior of pseudoephedrine, both alone and in combination with other drugs, has been further elucidated since Carki's study was submitted in 1976. The major determinate of the half-life of

pseudoephedrine is the pH of urine in which pseudoephedrine is excreted (urine flow also has an effect when the urine pH is above 7.0).[1,2] The observed half-life of pseudoephedrine has varied from 4 to 8 hours in normal individuals who are representative of the population at large.[1-4]

Appendix 3 contains computer simulations of steady state pseudoephedrine concentration profiles as a function of two dosing frequencies.* The simulations were generated from pharmacokinetic parameters determined in these more recent studies and assumed a daily adult dose of 240 mg. Please note that steady state was achieved with both regimens and, as a consequence, accumulation of pseudoephedrine over time is not a factor.

Table 1 compares the two simulations presented in Appendix 3.

TABLE 1 COMPARISON OF COMPUTER SIMULATIONS OF STEADY STATE PSEUDOEPHEDRINE CONCENTRATIONS AS A FUNCTION OF DOSAGE INTERVAL

Parameter	Method A - Dow Chemical		Method B - Burroughs Wellcome Co.	
	Every 6 hrs./24 hrs.	Every 4hrs/4x/day	Every 6 hrs/24 hrs	Every 4 hrs/4x/da
Half-life ($t_{\frac{1}{2}}$ hrs)	7.85	7.85	5.55	5.55
Maximum Concentration (Cmax - ng/ml)	595	646	340	420
Minimum Concentration (Cmin - ng/ml)	365	256	180	100
Swing (Cmax - Cmin)	230	390	160	320

* 60 mg of pseudoephedrine given: 1) every 6 hours over a 24 hour interval; or 2) every 4 hours, 4 times a day.

GP/rf/S1/K/3

It is apparent that the steady state profile is a delicate function of $t_{\frac{1}{2}}$ for pseudoephedrine. At the longer half-life depicted in Method A, the difference between the maximum achieved concentration of pseudoephedrine for dosage intervals of 60 mg every four hours for four doses is only 8.5% higher than the maximal concentration achieved at a dosage schedule of 60 mg every six hours for four doses. When the half-life is reduced in healthy male individuals excreting acid urine as depicted in Method B, the difference between the maximum concentration of pseudoephedrine achieved between the every four hour for four dose regimen as opposed to the every six hour for four dose regimen is 23%. It is noted however, that with a shorter half-life the 240 mg daily dose yields significantly lower mean and maximal concentration for pseudoephedrine when compared with the plots using a longer half-life. For each dosage schedule, the mean steady state level and area under the curve are identical.

These pharmacokinetic data clearly demonstrate that a flexible dose schedule every four to six hours is permissible and more reflective of the achievable blood levels than a fixed dosage of every six hours.

CORRELATION OF ADVERSE REACTIONS WITH PSEUDOEPHEDRINE PLASMA LEVELS

Recent studies afford a reasonable correlation between pseudoephedrine plasma levels and an adverse reaction profile. These are summarized below. Basically, these establish that while stimulation and small increases in pulse rate can be shown in carefully controlled studies of pseudoephedrine, steady state plasma levels consistent with those derived by simulation* do not result in clinically significant manifestations of these effects.

* Methods A & B in Appendix 3

Acute Studies

Two dose response studies involving single doses of pseudoephedrine have been completed. In an unpublished study, Bright, et al.[5] monitored selected cardiac and metabolic responses to pseudoephedrine as a function of exercise. While pseudoephedrine (60 or 120 mg) did not elicit subjective adverse effects or changes in blood glucose or insulin levels, it was responsible for several cardiovascular effects that appeared to be dose-dependent. Resting heart rate, time required to reach 85% maximal heart rates, and the amount of time required to reach pre-exercise heart rates were affected in such a manner, although the changes were not statistically significant. Sinus arrhythmias on the post exercise ECG increased as a function of dose with the 120 mg dose increasing the frequency significantly ($p < 0.05$). Blood pressures changed only in response to exercise and seemed to be unaffected by drug.

Empey, et al.[6] determined the cardiovascular effects of 15, 30, 60, 120 and 180 mg of pseudoephedrine. There was no difference between placebo and any dose of pseudoephedrine vis-a-vis the incidence and nature of adverse reactions. Small, but statistically significant increases in pulse and systolic blood pressure occurred after pseudoephedrine 120 and 180 mg, but not after pseudoephedrine 60, 30 or 15 mg. No significant effects were produced by any of the doses of pseudoephedrine with regard to diastolic blood pressure.

Chronic Studies

Three studies have provided information regarding steady state concentrations of pseudoephedrine and corresponding adverse reactions. In the Bye study cited by the FDA,[7] a sustained release formulation of 180 mg pseudoephedrine was administered twice daily for 14 days. Steady state plasma concentrations of pseudoephedrine ranged between 500 and 650 ng/ml. Such a regimen produced: 1) a small but statistically significant increase in heart rate which reached a plateau in 3 days; 2) some measurable sleep disturbance during the first 3 nights.

Pseudoephedrine - antihistamine combinations were employed in the other investigations. Perkins, et al.[8] reported a steady state pseudoephedrine concentration range of ∿ 350-550 ng/ml when the drug was combined with triprolidine (ACTIFED®). Adverse reactions attributable to pseudoephedrine (mostly stimulatory in nature) were rated as mild to moderate in severity and clinically insignificant. While statistically significant differences in pulse rates were observed at steady state when comparing the active treatment groups with placebo, they were not of such a magnitude as to be regarded as clinically significant (< 12 beats/min). Yacobi, et al.[4] found a pseudoephedrine steady state concentration range of ∿ 280-500 ng/ml when the drug was combined with chlorpheniramine. No increase in either the incidence or type of adverse reaction was observed.

COMPARISON OF ADULT DAILY DOSING FREQUENCIES IN TWO INGREDIENT OTC COUGH COLD COMBINATIONS INVOLVING PSEUDOEPHEDRINE

As previously mentioned, pseudoephedrine can be included in rational drug combinations (Appendix I). Table II compares the adult daily dosing frequencies of two ingredient combinations involving pseudoephedrine. It is apparent that a strict regimen of every 6 hours for pseudoephedrine presents a serious obstacle when combining it with drugs of different pharmacological classes. Four distinct dosing frequencies are recommended for the agents listed as "Ingredient B." In order to be combined with pseudoephedrine, they would all have to conform to the dosing frequency recommended by the Agency for this drug. This would militate against the consumer receiving the maximum therapeutic benefit from combination products.

DOSAGE RECOMMENDATIONS, DOSAGE UNITS* SOLD, ADVERSE REACTIONS AND OVER-DOSE FOR OVER THE COUNTER (OTC) SUDAFED, AUGUST 1, 1976-JULY 31,1980

Dosage Recommendations

Sudafed® Tablets contain 30 mg of pseudoephedrine HCl/tablet; Sudafed Syrup contains 30 mg of pseudoephedrine HCl/5 cc syrup. The recommended daily dose of pseudoephedrine HCl for the above interval was: Adults and children over 12 years of age, 60 mg every 4 hours. Children 6-12 years, 30 mg every 4 hours. For children, 2-5 years, 15 mg every 4 hours. Do not exceed 4 doses in 24 hours. For children under 2 years of age, give only as directed by a physician.

* Defined as the sum of individual tablets and individual cc's sold.

Dosage Units Sold

The quantities of OTC Sudafed sold are listed below.

OTC SUDAFED SOLD BETWEEN 8/1/76-7/31/80

DOSAGE FORM	QUANTITIES SOLD
a) Tablets	1,159,824,600
b) Syrup (Total cc's)	1,473,364,845
c) Dosage Units (a & b)	2,633,189,445

Adverse Reactions and Overdose

Reports of adverse reactions are provided in Table III. They represent all written or verbal reports submitted to Burroughs Wellcome Co. by health professionals. All reports were evaluated by the Burroughs Wellcome Product Surveillance Physician. The National Adverse Drug Reaction Dictionary "Co-Start" developed by the Department of Health, Education and Welfare was utilized as the thesarus. Those reactions which were considered to be of unlikely relationship to drug product are not included in the listings. Adverse reactions are grouped according to body system and are presented in descending order of frequency.

One overdose report involving the 30 mg tablet was received by Burroughs Wellcome. A depressed 37-year-old woman ingested 4500 mg/day of pseudo-ephedrine for a period of 4 years. The individual had a previous history of drug abuse. No symptoms were reported at this dosage level and the patient had been withdrawn at the time of reporting. This case was reported in Am. J. Psychiat. 136:1217, 1979.

It is obvious from the above, that the current dosing recommendations for OTC Sudafed are quite safe. This attests to the safety of the dosing recommendations being proposed in the current Petition as well.

GP/rf/S1/K/9

Dosage Units Sold

The quantities of Dow Novahistine OTC Pseudoephedrine (60mg) dose units sold:

OTC PSEUDOEPHEDRINE SOLD BETWEEN JULY 1975 AND JUNE 1980

DOSAGE FORM	QUANTITIES SOLD
a) Syrup	152,076,000
b) Tablets	12,780,000
c) Total (Total a + b)	164,856,000

Adverse Reactions

Reports of adverse reactions are provided in Table IV. They represent all written or verbal adverse drug reactions (ADR's) reported to October 1980. With the exception of one report of nervousness, insomnia and increased pulse rate in a 48-year-old, possibly pre-menopausal, female and a report of pupillary dilatation in children indicative of sympathomimetic action, there were no adverse pseudoephedrine-related side effects. None of the reactions was serious or life-threatening. The majority of the reported reactions were skin sensitivities most probably unrelated to pseudoephedrine.

Based on the number and types of reactions reported to us, it can be concluded that our pseudoephedrine-containing products are safe when given as directed in our current package literature.

DOSAGE RECOMMENDATIONS, DOSAGE UNITS* SOLD, ADVERSE REACTIONS AND OVER-DOSES FOR OVER-THE-COUNTER (OTC) CHLORTRIMETON-DECONGESTANT TABLETS, 8/75-12/31/80

DOSAGE RECOMMENDATIONS

Each CHLORTRIMETON-Decongestant (CTM-D) Tablet contains 4 mg. of chlorpheniramine maleate and 60 mg. of pseudoephedrine sulfate. The current recommended daily dosage** of CTM-D is as follows:

Adults and children over 12 years of age	1 tablet every 4 hrs., not to exceed 6 tablets/24 hrs.
Children 6-12 years of age	1/2 tablet every 4 hrs., not to exceed 3 tablets/24 hrs.
Children under the age of 6	There is no recommended OTC dosage; administered only as directed by a physician

OTC CHLORTRIMETON-DECONGESTANT SOLD BETWEEN 8/75 - 12/31/80

24	)	
48	)	411,000,000 tablets
24 x 4's	)	

ADVERSE REACTIONS

A summary of all adverse reactions received by Schering's Professional Services Department is provided in Table V. These represent reactions reported by either health professionals or consumers from the date of CTM-D's introduction in 1975 until the present time. One report, which raised the possibility of confusion

*Defined as the sum of the individual tablets sold.

between Chlortrimeton Allergy Tablets (which do not contain pseudo-ephedrine) and CTM-D has not been included.

With regard to the report submitted in 1977 in which the user complained of premature ventricular contractions, it should be noted that the consumption of an unknown quantity of caffeine sometime prior to the ingestion of CTM-D may have been a contributing factor.

OVER-DOSES

No over-doses of CTM-D have been reported.

Table II COMPARISON OF ADULT DAILY DOSING FREQUENCIES IN TWO INGREDIENT OTC COUGH COLD COMBINATIONS INVOLVING PSEUDOEPHEDRINE*

INGREDIENT A	INGREDIENT B
	ANALGESICS - ANTIPYRETICS**
	Aspirin, Acetaminophen, Calcium Carbaspirin, Choline Salicylate, Magnesium Salicylate, Sodium Salicylate - Every 4 hrs, not to exceed 6 doses in 24 hrs.
	ANTIHISTAMINES*
NASAL DECONGESTANT*	Brompheniramine Maleate, Chlorpheniramine Maleate, Diphenhydramine HCl, Doxylamine Succinate, Methapyrilene Preparations, Phenindamine Tartrate, Pheniramine Maleate, Thonzylamine HCl - Every 4-6 hrs. not to exceed 6 doses in 24 hrs.
Pseudoephedrine Preparations (HCl and SO4) - Every 6 hrs. not to exceed 4 doses in 24 hrs.	Promethazine HCl - Every 8-12 hrs. not to exceed 3 doses in 24 hrs.
	Pyrilamine Maleate - Every 6-8 hrs. not to exceed 4 doses in 24 hrs.
	ANTITUSSIVES*
	Codeine Preparations - Every 4-6 hrs. not to exceed 6 doses in 24 hrs.
	Dextromethorphan Preparations - Every 4 hrs. not to exceed 6 doses in 24 hrs. OR every 6-8 hrs. not to exceed 4 doses in 24 hrs.
	Diphenhydramine HCl - Every 4 hrs. not to exceed 6 doses in 24 hrs.
	EXPECTORANT*
	Guaifenesin - Every 4 hrs. not to exceed 6 doses in 24 hrs.

*Listed in Proposed Monograph for OTC Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products, Federal Register 41:38402 (September 9) 1976.

**Listed in Proposed Monograph for OTC Internal Analgesic, Antipyretic and Antirheumatic Products. Federal Register 42:35346 (July 8) 1977.

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Table III ADVERSE REACTIONS ASSOCIATED WITH OTC SUDAFED TABLETS AND SYRUP

Dermatological (14)*		General Body (3)		Metabolic/Hormonal (2)	
Rash	5	Anaphylactic Shock	1	Adrenergic Syndrome	1
Pruritis	2	Fever	1	Gout	1
Urticaria	2	Peripheral Edema	1		
Angioedema	2			Gastrointestinal (1)	
Maculopapular Rash	1	Respiratory (3)		Constipation	
Fixed Eruption	1	Dyspnea	2		
Skin Edema	1	Rhinorrhea	1		
Neurological (10)		Cardiovascular (2)			
Agitation	2	Tachycardia	1		
CNS Stimulation	2	Vasodilation	1		
Somnolence	1				
Convulsion	1				
Intracranial Hypertension	1	Genitourinary (2)			
Paresthesia	1	Urinary Retention	1		
Dizziness	1	Amenorrhea	1		
Insomnia	1				

*Number in parenthesis refer to total number of adverse reactions affecting a given body system.

TABLE IV
PSEUDOEPHEDRINE-CONTAINING PRODUCTS
ADVERSE DRUG REACTIONS (ADR's)*

Product	No. of ADR's	Year Reported	Description	Comments
NOVAHISTINE DMX	2	1976	Overdose (child)	Accidental
		"	Skin sensitivity (rash) (adolescent)	Possibly related to an ingredient
" "	3	1977	Pupillary dilatation (children)	Sympathomimetic effect
		"	Swelling of eyes (adult)	History of sensitivity to red dyes
		"	Burning throat (adult)	Possible contamination
" "	5	1978	Nervousness, insomnia, increased pulse rate (adult)	Pseudoephedrine-related (most likely)
		"	Lack of effectiveness (adult)	Subjective evaluation
		"	Sensitivity (child)	Undefined
		"	Skin sensitivity (hives) (1 child and 1 adult)	Possibly related to an ingredient
		"	Skin sensitivity (rash) (child)	History of sensitivity to penicillin
" "	2	1979	Allergic reaction (severe) (adolescent)	Also sensitive to ORNACOL®
		"	Distress - pain (adult)	Subjective - perhaps CNS stimulation
" "	2	1980	Allergic reaction (adult)	Possible sensitivity to an ingredient
		"	Skin sensitivity (rash) (adult)	Possible sensitivity to an ingredient
NOVAHISTINE DMX ADR's	14			

TABLE IV

PSEUDOEPHEDRINE-CONTAINING PRODUCTS (cont'd)
ADVERSE DRUG REACTIONS (ADR's)*

Product	No. of ADR's	Year Reported	Description	Comments
NOVAFED Liquid	3	1977	Skin sensitivity (child)	Perhaps due to tartrazine
		"	Diarrhea (2-3 children)	Concomitant antibiotics
		"	Cough and chest congestion	History of aspirin sensitivity
NOVAFED A Liquid	1	1975	Drowsiness (child)	Antihistamine-related
NOVAFED Liquids ADR's	4			
TOTAL ADR's (for our pseudoephedrine-containing drugs)	18			

*NOVAFED® Liquid, 30 mg/dose, was marketed October 1974, NOVAFED® and NOVAFED® A Liquids, 60 mg/dose, July 1975; NOVAHISTINE® DMX was marketed August 1975; NOVAHISTINE® Cough and Cold Formula and NOVAHISTINE® Sinus Tablets were marketed this year but no ADR's have been reported.

TABLE V

CHLORTRIMETON-D

ADVERSE DRUG REACTIONS

No. of ADR's	Year Reported	Description	Comments
1	1976	Palpitations/ chest pains	Patient's physician reported reaction "not drug-related"
1	1977	Premature ventricular contractions	Unknown quantity of caffeine consumed prior to ingestion of CTM-D
1	1977	Headache/high blood pressure	
1	1977	Dizziness/headache	
1	1979	Nausea/vomiting	
1	1979	Nausea	
1	1979	Exhaustion/depression Soporific effect	
1	1979	Unspecified side effects	
1	1980	Skin eruption	
1	1980	Unspecified "unpleasant" side effects	
1	1980	Exacerbated sinus condition	
1	1980	Exacerbated cold symptoms	